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The versatile nature of MIF
(macrophage migration inhibitory factor) in chronic lung diseases

Laura Florez Sampedro

The research described in this thesis was performed in the Groningen Research Institute of Pharmacy (GRIP) as a collaboration between Department of Chemical and Pharmaceutical Biology, Department of Pharmacokinetics, Toxicology and Targeting, and Department of Molecular Pharmacology.

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The versatile nature of MIF (macrophage migration inhibitory factor) in chronic lung diseases

PhD thesis

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the decision by the College of Deans.

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by

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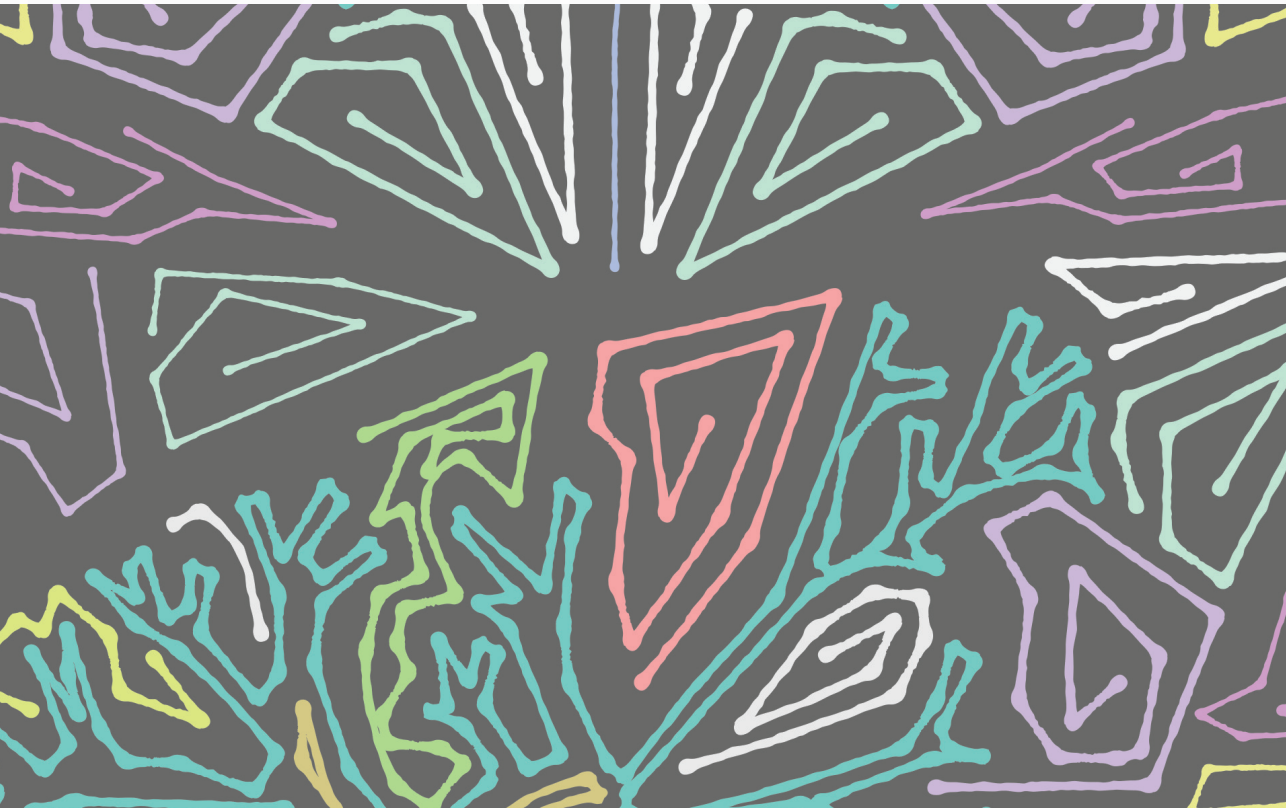
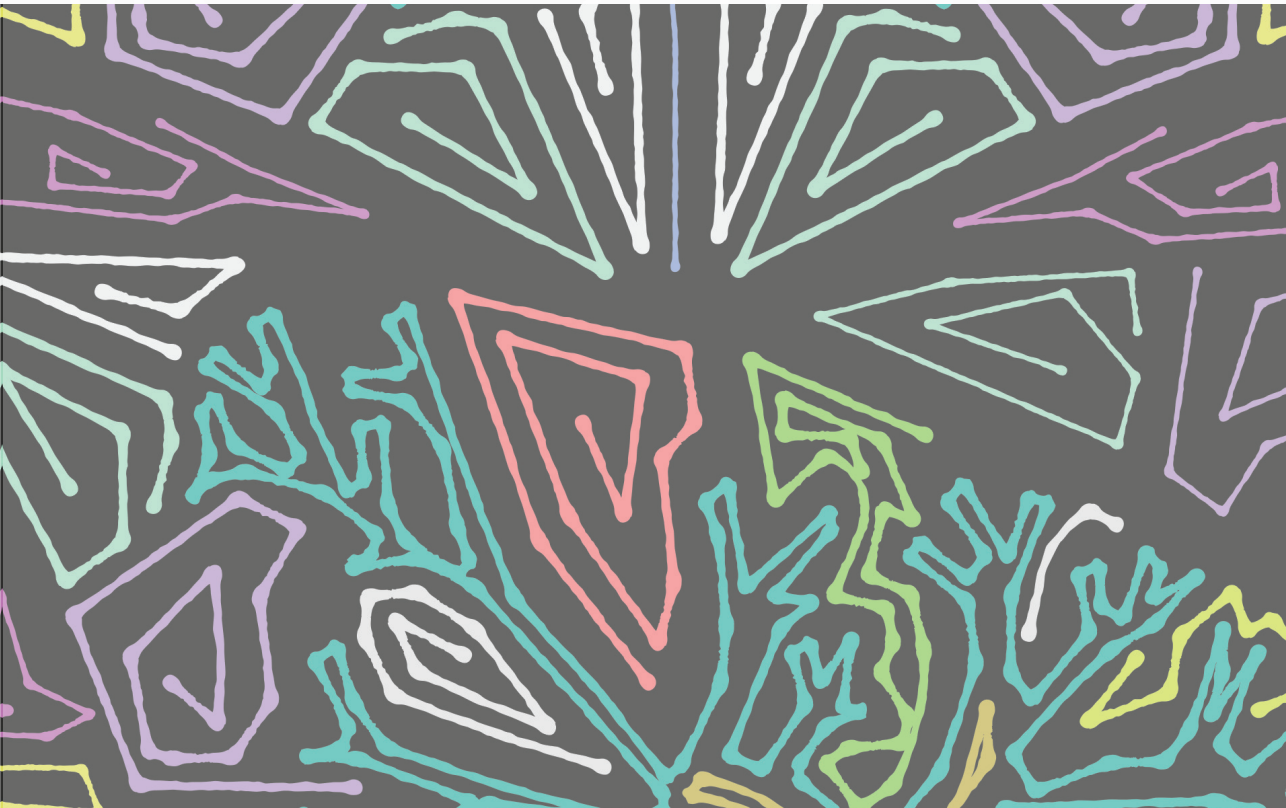
The patterns shown here (and used for the cover design) are inspired in the handcraft textiles known as ***Molas***, which are traditionally hand-made by the *Kuna* indigenous community in Colombia.



This thesis is dedicated to my family



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INTRODUCTION
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SCOPE OF THE THESIS

Chronic lung diseases are progressive conditions in which the function and the structure of the lung is altered, in most cases due to an unbalanced response to (long-term) exposure to toxic or allergenic airborne compounds. Two of the most common chronic lung diseases are chronic obstructive pulmonary disease (COPD) and asthma[1]. The pathogenic features and cellular processes involved in the development of COPD and asthma are explained in chapter 2 of this thesis.

The world health organization (WHO) estimated 251 million cases of COPD in 2016 and 3.17 million deaths caused by COPD globally in 2015[2]. It is estimated as the fourth cause of death worldwide[3]. Despite advancements in the treatment of COPD symptoms and the prevention of exacerbations, there are no therapeutic alternatives to stop disease progression and to date there is no cure for COPD.

According to recent WHO reports, asthma affects 235 million people worldwide, and it was estimated that there were 383 000 deaths due to asthma in 2015[4]. Although asthma does not kill to the extent of COPD, failure to use or access appropriate medication can lead to death. Moreover, asthma represents an additional economic and social burden leading it to rank 22nd worldwide in the list of diseases causing the highest number of years lost due to ill-health, disability or early death[5]. While appropriate management can usually control the disease and improve quality of life of a proportion of the patients, there is currently no cure for asthma and in up to 12% of the patients symptoms cannot be managed properly[6,7].

Considering that current treatment options for COPD and asthma have not decreased the prevalence, progression and burden of these diseases, a better understanding of the disease pathogeneses is needed. This will enable exploring new alternatives for the early diagnosis, accurate management or even curing these diseases.

Macrophage migration inhibitory factor (MIF)

Macrophage migration inhibitory factor (MIF) is a cytokine discovered in the late 1960's by Bloom and Bennett[8]. It was named based on the observation that sensitized lymphocytes produced a soluble mediator capable of inhibiting migration of macrophages. Although it was one of the first cytokines ever reported[9], many of the advances in MIF studies came decades later or are still in progress (Fig.1).

Although most reports refer to MIF as a proinflammatory cytokine, it is more accurate to define it as a pleiotropic cytokine due to the fact that it plays diverse roles on

mammalian cells and many of its effects described are not related to inflammation. In fact, despite the vast evidence of MIF's association with chronic and proinflammatory diseases, MIF does not always play a proinflammatory role in these conditions[10–12].

MIF has been associated with many lung conditions, including COPD and asthma[13]. Most studies in this area have found differences in MIF levels between COPD or asthma patients and control individuals. Mouse studies have also tested the effect of MIF inhibition or MIF deficiency on the development of pathological features. While the studies on MIF-deficient mice in COPD point to a protective role of MIF by preventing age-related or cigarette smoke-induced emphysema, the studies on asthma suggest a pathogenic role of MIF as MIF-deficient mice present with fewer characteristics of allergic inflammation. These mouse studies provide significant evidence of the possible role MIF plays in lung disease development *in vivo*, but considering that MIF function is also essential in healthy conditions, and MIF is constitutively expressed by several cell types in the lung, it is key to identify how MIF expression is regulated and how MIF influences the diseased lung. Identifying the role that MIF plays in lung diseases will contribute to the understanding of their complex pathogeneses and may open new avenues in the development of treatments for pulmonary conditions.

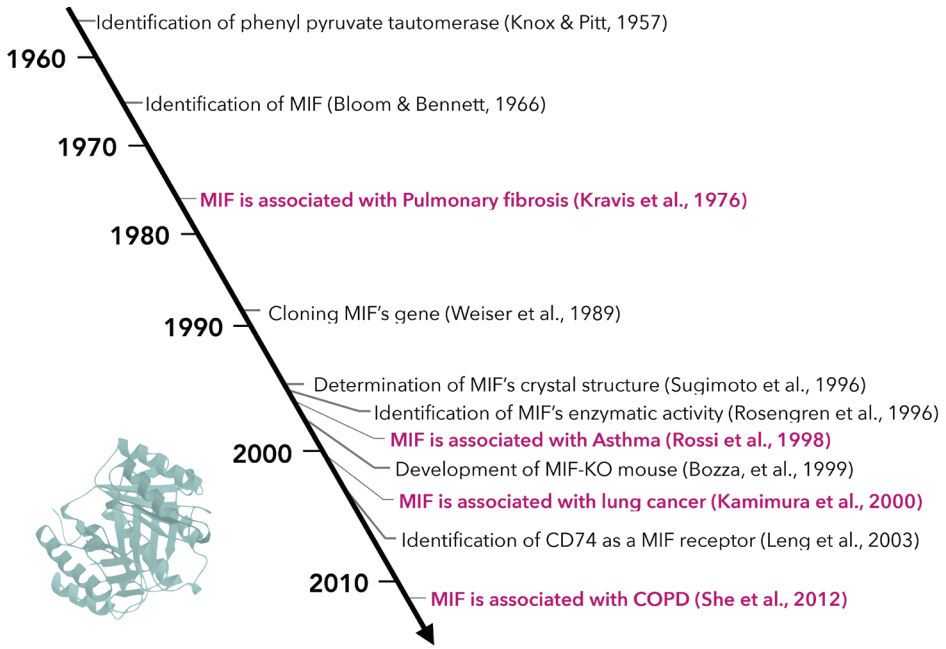

Figure 1. *Timeline of most important MIF discoveries (black) and first evidence of MIF's association with COPD, asthma, pulmonary fibrosis and lung cancer (In color. References: [8,14–23]).*

Scope of the thesis

The aim of this thesis was to study MIF expression and function in pulmonary diseases, mainly in COPD and asthma, in the context of cellular and innate immune responses.

First, in **chapter 1** we review the diversity of innate immune cells of myeloid origin that are involved in lung tissue repair and we illustrate how these cell types can contribute to the development of pulmonary fibrosis. This chapter establishes the basis for the cellular and pathological process involved in lung wound healing and the points that may be affected in the development of fibrosis in lung tissue.

In **chapter 2** we critically review the data available on MIF expression and function in chronic lung diseases with the aim of obtaining a better insight into the role MIF plays in the lung and in pulmonary diseases. Moreover, we illustrate the diverse roles of MIF in the pathogenesis of COPD, asthma, pulmonary fibrosis and lung cancer. Additionally, in this review we describe that MIF in the context of lung diseases has a stronger association with prorepair responses than with proinflammatory responses, demonstrating that MIF's role is not always proinflammatory as suggested before.

In **chapter 3** we investigate gene expression and genetic regulation of MIF family members in lung tissue in the context of COPD. We evaluate gene expression levels of MIF, DDT and DDTL in lung tissue samples of patients with and without COPD and assess whether their gene expression is regulated by single nucleotide polymorphisms (SNPs). We identify SNPs regulating MIF and DDTL expression and demonstrate that the direction of the SNP effect on MIF gene expression is dependent on the MIF splice variants analyzed. This chapter establishes that MIF gene expression is higher in COPD and can be influenced by SNPs, although not specifically in COPD.

In **chapter 4** we investigate the association of MIF with cellular senescence in the context of COPD. We study MIF expression during the development of cellular senescence in an *in vitro* model with a type 2 alveolar epithelial cell line and evaluate MIF expression and senescence markers in lung tissue from COPD and non-COPD patients. We demonstrate that MIF expression increases during the establishment of cellular senescence *in vitro* and that its presence is not essential for this phenomenon to take place, although it does influence the expression of certain senescence markers. We also describe significantly higher levels of MIF protein expression and senescence markers in lung tissue samples from COPD patients, compared to

control subjects. This chapter establishes that high MIF expression in COPD lung tissue may in part increase due to the cellular senescence that is characteristic of this condition.

In **chapter 5** we study the proliferation, recruitment and phenotype switching of macrophages during the development of house dust mite (HDM)-induced allergic lung inflammation. We demonstrate that during HDM-induced allergic lung inflammation the pool of polarized macrophages in the lung originates from local macrophages with little contribution from recruited monocytes. We show that the increase in YM1+ alveolar macrophages probably originates from trans-differentiating interstitial macrophages. This chapter establishes macrophage kinetics and origin during the development of allergic lung inflammation and constitutes the basis for the study of MIF family members and receptors during development of experimental asthma as described in chapter 6.

In **chapter 6** we investigate the kinetics and patterns of expression of MIF family members MIF and DDT and their receptor CD74 in lung tissue during the induction of HDM-induced allergic lung inflammation. We describe MIF, DDT and CD74 gene expression, and cellular patterns of MIF protein expression in lung tissue during the induction of allergic lung inflammation. Also, we confirm the patterns of MIF protein expression in single-cell sequencing data from lung samples from asthmatic patients and healthy individuals. This chapter defines the changes in cellular patterns of MIF expression from a healthy condition until development of allergic lung inflammation, providing more insight in possible pathogenic roles of MIF in asthma.

Finally, in the **discussion** chapter we examine our findings, their implications for chronic lung diseases, and the future perspectives for research on MIF function. We also condense the content of this thesis in a **summary.**

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